Chronic hepatitis virus infections in patients on renal replacement therapy

Fehr, T ; Ambuhl, P M

DOI: https://doi.org/10.1093/ndt/gfh080

8. Nishio I, Shima H, Tsuda K, Hano T, Masuyama Y. Relationship between the sympathetic nervous system and sodium potassium adenosine triphosphatase inhibitor in salt-sensitive patients with essential hypertension. *J Hypertens* 1988; 6 [Suppl]: S216–S218
9. Osanai T, Fujiwara N, Saitoh M *et al*. Relationship between salt intake, nitric oxide and asymmetric dimethylarginine and its relevance to patients with end-stage renal disease. *Blood Purif* 2002; 20: 466–468
10. Aviv A. Salt consumption, reactive oxygen species and cardiovascular ageing: a hypothetical link. *J Hypertens* 2002; 20: 555–559
11. Zalba G, San Jose G, Moreno MU *et al*. Oxidative stress in arterial hypertension: role of NAD(P)H oxidase. *Hypertension* 2001; 38: 1395–1399
12. Wang HD, Johns DG, Xu S, Cohen RA. Role of superoxide anion in regulating pressor and vascular hypertrophic response to angiotensin II. *Am J Physiol Heart Circ Physiol* 2002; 282: H1697–H1702
13. Ritz E, Haxsen V. Angiotensin II and oxidative stress: an unholy alliance. *J Am Soc Nephrol* 2003; 14: 2985–2987
14. Lacy F, O'Connor DT, Schmid-Schonbein GW. Plasma hydrogen peroxide production in hypertensives and normotensive subjects at genetic risk of hypertension. *J Hypertens* 1998; 16: 291–303
15. Koomans HA, Roos JC, Boer P, Geyskes GG, Mees EJ. Salt sensitivity of blood pressure in chronic renal failure. Evidence for renal control of body fluid distribution in man. *Hypertension* 1982; 4: 190–197
16. Weidmann P, Maxwell MH. The renin-angiotensin-aldosteron system in terminal renal failure. *Kidney Int* 1975; 8 [Suppl]: 219–234
17. Leenen FH, Galla SJ, Geyskes GC, Murdaugh HV, Shapiro AP. Effects of hemodialysis and saline loading on body fluid compartments, plasma renin activity, and blood pressure in patients on chronic hemodialysis. *Nephron* 1977; 18: 93–100
18. Klein IH, Ligtenberg G, Neumann J, Oey PL, Koomans HA, Blankestijn PJ. Sympathetic nerve activity is inappropriately increased in chronic renal disease. *J Am Soc Nephrol* 2003; 14: 3239–3244
19. Ozkahya M, Ok E, Cirit M *et al*. Regression of left ventricular hypertrophy in haemodialysis patients by ultrafiltration and reduced salt intake without antihypertensive drugs. *Nephrol Dial Transplant* 1998; 13: 1489–1493
20. Luik AJ, Charra B, Katzarski K *et al*. Blood pressure control and hemodynamic changes in patients on long time dialysis treatment. *Blood Purif* 1998; 16: 197–209
21. Nesrallah G, Suri R, Moist L, Kortas C, Lindsay RM. Volume control and blood pressure management in patients undergoing quotidian hemodialysis. *Am J Kidney Dis* 2003; 42 [Suppl 1]: 13–17
22. Moret K, Hassell D, Kooman JP *et al*. Ionic mass balance and blood volume preservation during a high, standard, and individualized dialysate sodium concentration. *Nephrol Dial Transplant* 2002; 17: 1463–1469
23. Krautzig S, Janssen U, Koch KM, Granolleras C, Shaldon S. Dietary salt restriction and reduction of dialysate sodium to control hypertension in maintenance haemodialysis patients. *Nephrol Dial Transplant* 1998; 13: 552–553
24. Tobian L. Dietary sodium chloride and potassium have effects on the pathophysiology of hypertension in humans and animals. *Am J Clin Nutr* 1997; 65 [Suppl 2]: 606S–611S
25. Safar ME, Thuilliez C, Richard V, Benetos A. Pressure-independent contribution of sodium to large artery structure and function in hypertension. *Cardiovasc Res* 2000; 46: 269–276
26. Schmieder RE, Messerli FH, Ruddel H *et al*. Sodium intake modulates left ventricular hypertrophy in essential hypertension. *J Hypertens* 1988; 6 [Suppl]: S148–S150
27. Draaijer P, Kool MJ, van Bortel LM *et al*. Vascular compliance in sodium-sensitive and sodium-resistant borderline hypertensive patients. *Kidney Int* 1995; 47: 169–176
28. Luik AJ, Spek JJ, Charra B, van Bortel LM, Laurent G, Leunissen KM. Arterial compliance in patients on long-treatment-time dialysis. *Nephrol Dial Transplant* 1997; 12: 2629–2632
29. Chan CT, Floras JS, Miller JA, Richardson RM, Pierratos A. Regression of left ventricular hypertrophy after conversion to nocturnal hemodialysis. *Kidney Int* 2002; 61: 2235–2239
30. Jonsson O, Lundgren Y, Wennergren G. The distribution of sodium in aortic walls from spontaneously hypertensive and normotensive rats. *Hypertension* 1980; 2: 192–197
31. Ruiz-Ortega M, Lorenzo O, Rupérez M, König S, Wittig B, Egido J. Angiotensin II activates nuclear transcription factor κB through AT_1 and AT_2 in vascular smooth muscle cells: molecular mechanisms. *Circ Res* 2000; 86: 1266–1272

Nephrol Dial Transplant (2004) 19: 1049–1053
DOI: 10.1093/ndt/gfh080
Advance Access publication 5 March 2004

Chronic hepatitis virus infections in patients on renal replacement therapy

Thomas Fehr and Patrice M. Ambühl

Division of Nephrology, Department of Internal Medicine, University Hospital, Zurich, Switzerland

Keywords: diagnosis; dialysis; hepatitis; therapy; transplantation

Correspondence and offprint requests to: Thomas Fehr, MD, Transplantation Biology Research Center, Massachusetts General Hospital, MGH East CNY 149, 13th street, Boston, MA 02129, USA. Email: thomas.fehr@tbrc.mgh.harvard.edu

The magnitude of the problem

Hepatitis B (HBV) and C (HCV) virus infections represent a major problem in dialysis patients and renal allograft recipients.

(i) They cause renal failure due to glomerulonephritis, which may recur in the renal transplant [1].
(ii) Patients with chronic renal failure have acquired hepatitis virus infection via blood transfusions, which were necessary to treat hyporegenerative renal anaemia. With the advent of recombinant human erythropoietin, this has now become a minor source of transmission. However, repetitive invasive diagnostic and therapeutic interventions still cause major bleeding episodes in the context of uraemia.
(iii) HBV and HCV infections are difficult to treat because of the limited efficacy and a high rate of side effects of the available drugs.
(iv) No HCV vaccination is available yet.

Prevalence of HBV and HCV infection

The prevalence of HBV and HCV infection in patients on renal replacement therapy varies considerably among different areas of the world (Table 1) [2]. It is usually similar in dialysis patients and renal transplant recipients, but high compared with the general population, indicating that infections occur mainly during the time on dialysis. Two epidemiological patterns can be observed. First is a geographical distribution, which reflects the disease burden in the general population. It is higher in the Middle East and Far East compared with Western countries. Within Europe, a north–south gradient of increased prevalence towards the latter has been reported. Second, countries with a lower socio-economic status have a higher prevalence of HBV and HCV infection among dialysis patients, indicating lower resources for maintenance of haemodialysis units, HBV vaccination programmes and erythropoietin treatment. Repetitive blood transfusions are the single most important factor for hepatitis virus transmission, whereas infection through contaminated haemodialysis equipment occurs less frequently [3]. Finally, patient to patient transmission of hepatitis virus with transplanted organs has been reported [4].

Table 1. Prevalence of HBV and HCV infection in patients on renal replacement therapy[a]

	Haemodialysis patients		Renal transplant recipients	
	HBV	HCV	HBV	HCV
Europe				
Netherlands		2.9–3.4%		
Switzerland	1.5%	5%	2.4%	7.2%
Germany	4.6%	7%	3%	13%
Spain	2.8%	19–30%		46%
Italy	4.3%	47–60%	4%	33%
America				
USA	2.4%	8.4%		10.3%
Brazil	12–45%	11–26%	27%	40%
Middle/Far East				
Israel		18%		12.3%
Syria		49%		
Saudi Arabia		68%		
India		4–36%		37%
China		30%	15%	50%
Taiwan	22%	34%	31%	39%
Japan	2.1%	27%		21.7%
Africa				
Tunisia	53%	42%		

[a]All data are retrieved from recent publications (<10 years old). However, the actual prevalence in some of the countries might have changed due to specific health care programmes. A list of the references is available from the authors upon request.

Diagnostic approach

Therapeutic options for HBV and HCV infection are limited in patients on renal replacement therapy. Therefore, a great effort should be made towards early diagnosis in the course of chronic renal insufficiency.

Diagnosis of infection

HBV infection

Patients at risk are screened by detection of HBV surface antigen (HBsAg) in serum. Positive HBsAg indicates HBV infection, but it is not equivalent with active viral replication, which is assessed by qualitative (HBeAg) or quantitative tests [HBV DNA polymerase chain reaction (PCR), hybridization]. We suggest the use of a DNA-based test to assess HBV replication for two reasons. (a) Guidelines for therapy decisions are based on these tests. Whether PCR has any advantage over hybridization is unresolved. Low PCR titres ($<1\times10^6$ copies/ml) are usually associated with negative hybridization tests. A benefit of therapy in these patients has not been established. (b) A negative HBeAg test either results from absence of replication or from a mutation of the virus in the pre-core region, which is often associated with even higher viral titres [5].

HCV infection

Screening is performed by anti-HCV antibody detection in serum. Serology is associated with problems of specificity and sensitivity in patients on renal replacement therapy. *False-positive results* may result from polyclonal B cell stimulation in the context of other infections (i.e. human immunodeficiency virus) or autoimmune diseases (i.e. systemic lupus erythematosus) [6,7]. This problem has been overcome with the introduction of newer generation anti-HCV screening tests [8]. *False-negative results* are also observed in dialysis patients. A recent report from Israel indicated that 9% of seronegative haemodialysis patients had positive HCV RNA tests using PCR techniques [9].

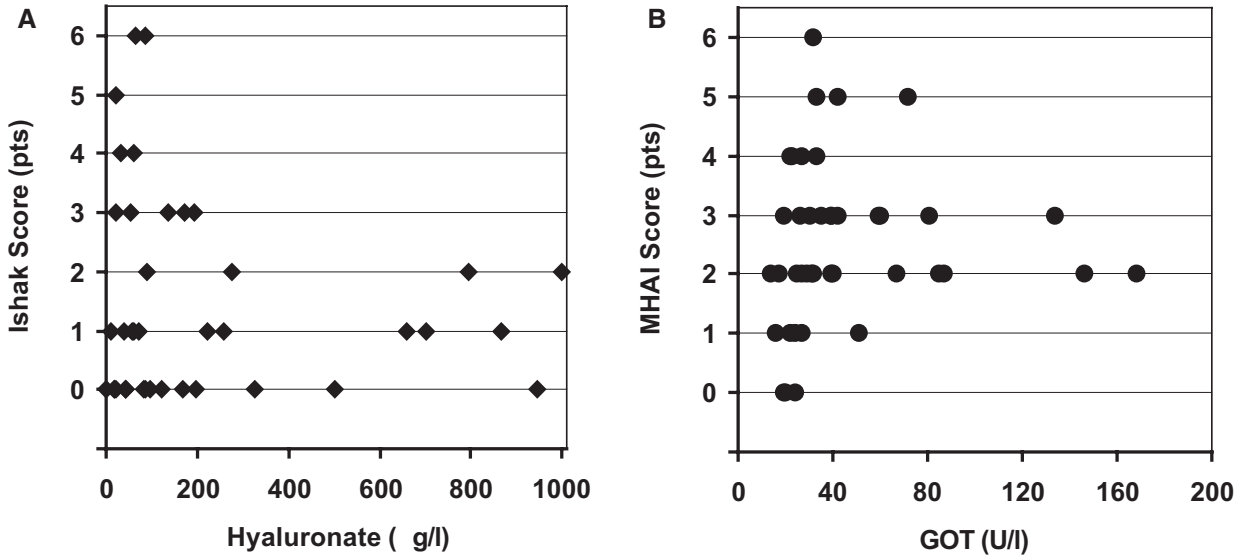

Fig. 1. Correlation of histological and biochemical parameters in 41 renal allograft recipients with chronic HBV or HCV infection. Reprinted from [10] with permission from the National Kidney Foundation. (**A**) Correlation of the fibrosis marker hyaluronate with the histological score of liver fibrosis according to Ishak (scores of 5 and 6 reflect focal and diffuse cirrhosis, respectively; 6 is the maximum score). (**B**) Correlation of serum glutamate oxaloacetate transaminase (GOT) concentration at the time of biopsy with the histological score of necroinflammatory liver lesions (MHAI; maximum score is 18).

This finding profoundly influences infection containment programmes in haemodialysis units. We suggest that all *patients with advanced renal insufficiency* receive serological HCV screening. In case of a positive result, it should be followed by HCV RNA PCR to determine the viral load, which is the basis for therapeutic decisions. Usually ~80–90% of patients harbour replicating virus, whereas the remaining have successfully cleared it [10]. All *patients entering a renal replacement programme (dialysis or renal transplantation)* should at least undergo one HCV RNA PCR test, irrespective of their serological status, since active viral replication has profound individual and epidemiological implications.

Assessment of liver disease severity

A number of studies have tried to assess the severity of liver disease by serological tests in order to avoid liver biopsy, which has an increased risk of bleeding in uraemic patients and haemodialysis patients receiving regular anticoagulation therapy with heparin. The most promising combination of six markers has been reported as FibroTest® [11], but it remains to be evaluated in patients on immunosuppressive therapy or dialysis. We recently compared serum concentrations of transaminases and hyaluronate (a fibrosis marker) with liver biopsy results in over 40 renal allograft recipients and found no correlation (Figure 1) [10]. Therefore, we suggest that a liver biopsy is performed in all patients with moderate to severe renal failure and patients on renal replacement therapy, if they have replicating HBV or HCV infection with elevated transaminases and if antiviral therapy is feasible and accepted by the patient in case of positive histological findings. In patients with a high risk of bleeding, prophylaxis with deamino-D-arginine vasopressin for uraemic platelet dysfunction is recommended [12] and a transjugular biopsy approach should be evaluated.

HBV and HCV infection harbour the risk of developing hepatocellular carcinoma. Therefore, and irrespective of other therapeutic decisions, these patients should be followed by twice yearly ultrasound of the liver and alpha-fetoprotein determination.

Therapeutic approach

Therapeutic decisions for HBV and HCV infection are based on three requirements: (A) demonstration of viral replication; (B) biochemical evidence of hepatitis by repeatedly elevated transaminase levels ($>1.5 \times$ upper normal value); and (C) liver biopsy showing either mild inflammation and/or fibrosis. A compilation of therapeutic options in renal patients is given in Table 2.

Role and risks of interferon therapy

The cornerstone of standard therapies for HBV and HCV infection is interferon-α. Important side effects are myelotoxicity and neurological/psychiatric symptoms. Therefore, patients with neurological/psychiatric disorders and patients with haematological disorders are usually excluded from therapy. In renal patients, anaemia should be treated with erythropoietin, iron and vitamin supplements prior to interferon therapy.

Table 2. Therapeutic options for HBV and HCV infection in renal patients

Patient with	Chronic renal failure	Dialysis	Renal allograft
HBV infection			
Prevention with vaccine	Yes (higher dose)	Yes (higher dose)	Yes
First-line treatment	Interferon-α	Interferon-α	Lamivudine
Second-line treatment[a]	Lamivudine	Lamivudine	Adefovir dipivoxil
	Adefovir dipivoxil	Adefovir dipivoxil	Combination of both?
	Combination of both?	Combination of both?	
HCV infection			
Prevention with vaccine	Not available	Not available	Not available
First-line treatment	PEG-interferon + ribavirin	PEG-interferon ± ribavirin[b]	No treatment
Second-line treatment[a]	?	?	PEG-interferon/ribavirin
			Ribavirin + amantadine?

[a]In case of contraindications to interferon or failure of first-line treatment. [b]Only with monitoring of ribavirin blood levels.

Patients with autoimmune disorders should be meticulously followed for symptoms and signs of their primary disease, since interferon-α may cause flare-ups. On the other hand, antiviral therapy is the standard treatment for virus-induced autoimmunity, such as HCV-mediated cryoglobulinaemia.

Several reports indicate that interferon-α, as a non-specific immunostimulator, causes acute humoral or cellular rejection of renal allografts in ~20–30% of cases [13–15]. In some cases, rejection could be successfully treated by standard rejection treatment, including steroids and anti-T cell antibodies [16]. Based on these findings we suggest that a therapeutic strategy *without* interferon-α should primarily be chosen in renal transplant patients. If everything fails, interferon-α may be considered upon informed consent of the patient regarding the risk of allograft rejection, necessitating intensified immunosuppressive treatment and potential graft loss [17].

Specific therapeutic options in different patient groups

HBV infection

The primary goal is *prevention*. A highly efficient recombinant vaccine for HBV is available. Since the response rate in patients with advanced renal failure and dialysis patients is impaired [18], vaccination should be performed at an early stage of renal insufficiency. For haemodialysis patients, a special vaccine at a 4-fold higher dose can be used.

In case of replicating HBV infection with histological alterations, antiviral therapy should be considered. In *patients with advanced renal failure and in dialysis patients* – especially transplant candidates – a therapeutic trial with interferon-α should be performed, since it offers the best chance of cure. In case of treatment failure or serious contraindications, the antiviral drugs lamivudine and adefovir dipivoxil may be considered [19]. Whereas lamivudine has been the standard treatment for years, adefovir dipivoxil has only recently proven to be effective against lamivudine-resistant HBV. Combination treatment has comparable primary response rates, but a lower rate of therapy failure due to lamivudine resistance from monotherapy. However, no controlled trials with adefovir dipivoxil have been performed in patients with advanced renal insufficiency or in renal allograft recipients. In transplant candidates with contraindications for interferon-α, the risk of replicating HBV infection has to be balanced carefully against the risk of developing lamivudine resistance with the loss of a treatment option after transplantation.

For *patients with a renal allograft* we recommend first-line treatment with lamivudine, thus, avoiding the risk of interferon-induced rejection. A recent report showed excellent response rates (biochemical: 80–100%; virological: 67–100%) [20]. In case of treatment failure or development of lamivudine resistance, a trial with adefovir dipivoxil or a combination of both antiviral drugs can be performed and the patient should be followed together with an experienced hepatologist.

HCV infection

Therapy of HCV infection in *renal allograft recipients* is difficult since interferon should be avoided and ribavirin alone has failed to induce a sustained virological response or amelioration of liver histology [21]. Furthermore, our recent report on liver biopsies in 23 renal allograft recipients with chronic HCV infection showed that none of them had developed cirrhosis after a mean follow-up of 12 years post-transplantation [10]. This indicates that part of the liver damage may be induced by immunological mechanisms rather than by HCV itself [22] and, hence, may even improve under immunosuppressive therapy. Therefore, renal allograft recipients with replicating HCV infection should *not* receive therapy, except for patients included in clinical studies and individual cases with very aggressive disease [17].

Patients with moderate to severe renal insufficiency are treated according to standard protocols, including pegylated (PEG-)interferon-α and ribavirin [23].

In *dialysis patients*, ribavirin should only be given when blood levels can be monitored, as severe haemolytic anaemia may develop due to overdosing [24,25]. Sustained virological response is lower with interferon-α monotherapy. However, two recent reports showed a response rate of 40–60% in this population. All patients that were subsequently transplanted remained HCV RNA PCR-negative, indicating permanent viral clearance [26], and only one developed recurrent glomerulonephritis [27].

Conclusion

Chronic HBV and HCV infection in patients on renal replacement therapy represent a major medical and epidemiological challenge to treating physicians. Due to the substantial morbidity and mortality associated with these conditions, special consideration regarding monitoring and evaluation of therapeutic options is mandatory. Unfortunately, medical therapy is limited in these patients, which puts even more emphasis on prophylactic measures, such as early vaccination against HBV, and prevention of viral transmission during time on dialysis.

Conflict of interest statement. None declared.

References

1. Denton MD, Singh AK. Recurrent and *de novo* glomerulonephritis in the renal allograft. *Semin Nephrol* 2000; 20: 164–175
2. Burdick RA, Bragg-Gresham JL, Woods JD *et al*. Patterns of hepatitis B prevalence and seroconversion in hemodialysis units from three continents: the DOPPS. *Kidney Int* 2003; 63: 2222–2229
3. Huraib SO. Hepatitis C in dialysis patients. *Saudi Med J* 2003; 24 [Suppl 2]: S123
4. Roth D. Hepatitis C virus: the nephrologist's view. *Am J Kidney Dis* 1995; 25: 3–16
5. Preikschat P, Gunther S, Reinhold S *et al*. Complex HBV populations with mutations in core promoter, C gene, and pre-S region are associated with development of cirrhosis in long-term renal transplant recipients. *Hepatology* 2002; 35: 466–477
6. Hayashi PH, Flynn N, McCurdy SA *et al*. Prevalence of hepatitis C virus antibodies among patients infected with human immunodeficiency virus. *J Med Virol* 1991; 33: 177–180
7. Kowdley KV, Subler DE, Scheffel J, Moore B, Smith H. Hepatitis C virus antibodies in systemic lupus erythematosus. *J Clin Gastroenterol* 1997; 25: 437–439
8. Abdel-Hamid M, El Daly M, El Kafrawy S *et al*. Comparison of second- and third-generation enzyme immunoassays for detecting antibodies to hepatitis C virus. *J Clin Microbiol* 2002; 40: 1656–1659
9. Hanuka N, Sikuler E, Tovbin D *et al*. Hepatitis C virus infection in renal failure patients in the absence of anti-hepatitis C virus antibodies. *J Viral Hepat* 2002; 9: 141–145
10. Fehr T, Riehle HM, Nigg L *et al*. Evaluation of hepatitis B and hepatitis C virus-infected renal allograft recipients with liver biopsy and noninvasive parameters. *Am J Kidney Dis* 2003; 42: 193–201
11. Imbert-Bismut F, Ratziu V, Pieroni L *et al*. Biochemical markers of liver fibrosis in patients with hepatitis C virus infection: a prospective study. *Lancet* 2001; 357: 1069–1075
12. Mannucci PM, Remuzzi G, Pusineri F *et al*. Deamino-8-D-arginine vasopressin shortens the bleeding time in uremia. *N Engl J Med* 1983; 308: 8–12
13. Rostaing L, Izopet J, Baron E *et al*. Treatment of chronic hepatitis C with recombinant interferon alpha in kidney transplant recipients. *Transplantation* 1995; 59: 1426–1431
14. Durlik M, Gaciong Z, Rowinska D *et al*. Long-term results of treatment of chronic hepatitis B, C and D with interferon-alpha in renal allograft recipients. *Transplant Int* 1998; 11 [Suppl 1]: S135–S139
15. Baid S, Tolkoff-Rubin N, Saidman S *et al*. Acute humoral rejection in hepatitis C-infected renal transplant recipients receiving antiviral therapy. *Am J Transplant* 2003; 3: 74–78
16. Ichikawa Y, Kyo M, Hanafusa T *et al*. A 20-year case study of a kidney transplant recipient with chronic active hepatitis C: clinical course and successful treatment for late acute rejection induced by interferon therapy. *Transplantation* 1998; 65: 134–138
17. Tang S, Cheng IK, Leung VK *et al*. Successful treatment of hepatitis C after kidney transplantation with combined interferon alpha-2b and ribavirin. *J Hepatol* 2003; 39: 875–878
18. Eardley KS, Jones HE, Osman H, Smith SA. Efficacy of the accelerated hepatitis B vaccination schedule used in haemodialysis patients post-exposure to virus: a single-centre experience. *Nephrol Dial Transplant* 2002; 17: 1982–1987
19. Dando T, Plosker G. Adefovir dipivoxil: a review of its use in chronic hepatitis B. *Drugs* 2003; 63: 2215–2234
20. Fabrizi F, Lunghi G, Poordad FF, Martin P. Management of hepatitis B after renal transplantation: an update. *J Nephrol* 2002; 15: 113–122
21. Kamar N, Sandres-Saune K, Selves J *et al*. Long-term ribavirin therapy in hepatitis C virus-positive renal transplant patients: effects on renal function and liver histology. *Am J Kidney Dis* 2003; 42: 184–192
22. Chang KM, Rehermann B, Chisari FV. Immunopathology of hepatitis C. *Springer Semin Immunopathol* 1997; 19: 57–68
23. Fried MW, Shiffman ML, Reddy KR *et al*. Peginterferon alfa-2a plus ribavirin for chronic hepatitis C virus infection. *N Engl J Med* 2002; 347: 975–982
24. Bruchfeld A, Stahle L, Andersson J, Schvarcz R. Interferon and ribavirin therapy in dialysis patients with chronic hepatitis C. *Nephrol Dial Transplant* 2001; 16: 1729
25. Fabrizi F, Martin P, Ponticelli C. Hepatitis C virus infection and renal transplantation. *Am J Kidney Dis* 2001; 38: 919–934
26. Kamar N, Toupance O, Buchler M *et al*. Evidence that clearance of hepatitis C virus RNA after alpha-interferon therapy in dialysis patients is sustained after renal transplantation. *J Am Soc Nephrol* 2003; 14: 2092–2098
27. Cruzado JM, Casanovas-Taltavull T, Torras J *et al*. Pretransplant Interferon prevents hepatitis C virus-associated glomerulonephritis in renal allografts by HCV-RNA clearance. *Am J Transplant* 2003; 3: 357–360